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10/528,344	11/08/2005	Pierre Falson	034404-001	5049

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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/528,344	FALSON ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *13,14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,15 and 17-22* is/are rejected.

7)☒ Claim(s) *10,11,16 and 23-25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received October 22, 2007.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-25 and the species of: Hepatitis C virus, Toxic protein of SEQ ID NO: 2, Soluble protein of SEQ ID NO: 37, Fusion protein of SEQ ID NO: 47 and Bacterial expression vector of SEQ ID NO: 41 are acknowledged. Claims 13, 14, and 26 are withdrawn because the claims are drawn to the non-elected invention. It is understood that the elected SEQ ID NO: 41 encodes the pGEXKT plasmid and thus the pGEXKT plasmid is presently examined. Therefore plasmids pT7-7 and pET32a are not examined in the present Office action. Claims 13 and 14 are withdrawn because the claims are drawn to a pT7-7 plasmid encoded by the non-elected sequences: SEQ ID NO: 44 and SEQ ID NO: 45. Claim 6 is examined because it is understood that SEQ ID NO: 4 recited in claim 6 encodes the toxic protein of the elected SEQ ID NO: 2.

Applicant argues that Wang et al., cited in the restriction requirement of August 20, 2007 does not teach or suggest the expression system for the expression of toxic membrane proteins. The Office agrees with the Applicant that Wang et al. does not teach the special technical feature of the present invention. However the special technical feature of the invention is taught in the prior art by Chan et al. (EP 0 212 532) as evidenced by Weiner et al. (US Patent 6,881,558 B1) as discussed in the rejection under the 35 U.S.C. 102(b) below and as taught by Bolling et al. (US Patent 5,322,769) in view of DeBeck et al. (Journal of Biological Chemistry, 2000, Vol. 275, p. 31428-31437, in IDS of 6/23/2005) Caccaglione et al. (Virus Genes, 2000, Vol. 21, p.

223-226, in IDS of 6/23/2005) and Arechega et al. (FEBS, 2000, Vol. 482, p. 215-219) as discussed under the 35 U.S.C. 103(a) rejection below. Thus because the art teaches the special technical feature of the present invention, the inventions listed in groups I and II do not relate to a single general inventive concept and thus the restriction requirement is deemed proper and is made FINAL.

Claims 1-12, and 15-25 are under examination in the present Office action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/23/2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Objections

Claims 5, 6, 10, 11, 16, and 23-25 are objected to because of the following informalities: Claims recite "ID No. (...)". The claims should recite "SEQ ID NO: (...)". Additionally claims recite "ID No. (...) of the attached sequence listing" and this recitation is unnecessary because the claims should be complete on their own. Appropriate correction is required.

Claims 10, 11, 16, and 23-25 are objected to because the claims depend from rejected claim 1.

Specification

The specification is objected to for referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See Figure 1 of Drawings. The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

It is also noted that the peptide sequence represented in Figure 1 as TME2 is not identical with SEQ ID NO: 2 of the present sequence listing or the specification (see [0024]), because the TME2 of the drawings lacks the M (Methionine) on the N-terminus.

The disclosure is objected to because it contains an **embedded hyperlink** and/or other form of browser-executable code on page 19 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 12, 17-22 are rejected under 35 U.S.C. 102 (b) as being anticipated by Bolling et al. (US Patent 5,322,769) as evidenced by Weiner et al. (US Patent 6,881,558 B1).

Claims are drawn to an expression system and a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding a toxic membrane protein or a domain of a toxic membrane protein of a viral envelope cloned into a plasmid. The claims are also drawn to methods for producing a toxic protein by genetic recombination.

Bolling et al. disclose a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding the HIV gp41 membrane domain and a method of producing the HIV gp41 membrane protein by genetic recombination in E. coli (see Examples 4 and 5). The Weiner et al. Patent is cited to provide evidence that the HIV envelope protein comprising a membrane domain was known to be toxic to E. coli genetically engineered to express the HIV envelope protein, at the time the invention was made (see column 1, lines 15-26). Thus, Bolling's envelope protein comprising a membrane protein is toxic to E. coli. Thus by this disclosure Bolling et al. anticipate the present claims.

Claims 1-3, 12, 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al. (EP 0 212 532) as evidenced by Weiner et al. (US Patent 6,881,558 B1).

Claims are drawn to an expression system and a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding a toxic membrane protein or a domain of a toxic membrane protein of a viral

envelope cloned into a plasmid. The claims are also drawn to methods for producing a toxic protein by genetic recombination.

Chan et al. disclose a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding an envelope protein of HIV and a method of producing the HIV envelope protein by genetic recombination in E. coli (see claims 1-15, page 8, line 10, lines 18-22, page 13, lines 20-35, page 14, lines 26-36, and page 15, lines 1-5 and Example 7). Because the envelope protein of HIV comprises membrane protein gp41, the expression vector disclosed by Chan et al. encodes a membrane protein and a domain of a membrane protein as required by the present claims. The Weiner et al. Patent is cited to provide evidence that the HIV envelope protein comprising a membrane domain was known to be toxic to E. coli genetically engineered to express the HIV envelope protein at the time the invention was made (see column 1, lines 15-26). Thus, Chan's envelope protein comprising a membrane protein is toxic to E. coli. Thus by this disclosure Chan et al. anticipate the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolling et al. (US Patent 5,322,769) as applied to claim 1 and further in view of De Beeck et al.

(Journal of Biological Chemistry, 2000, Vol. 275, p. 31428-31437, in IDS of 6/23/2005) and Arechaga et al. (FEBS, 2000, Vol. 482, p. 215-219) as evidenced by Caccaglione et al. (Virus Genes, 2000, Vol. 21, p. 223-226, in IDS of 6/23/2005).

Claims are drawn to an expression system and a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding a toxic membrane protein or a domain of a toxic membrane protein of a viral envelope cloned into a plasmid. The claims are also drawn to methods for producing a toxic protein by genetic recombination. The toxic protein is a transmembrane protein of the hepatitis C virus. It is noted that claim 5 recites "**a protein** of sequence ID No. 2". A protein is considered to be a part of SEQ ID NO: 2 of at least 2 amino acids, thus the claim reads on any peptide consisting of at lest two amino acids comprises within the SEQ ID NO: 2.

Bolling et al. teach a bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding the HIV gp41 membrane domain and a method of producing the HIV gp41 membrane protein by genetic recombination in E. coli (see Example 4 and Example 5).

Bolling et al. do not expressly teach HCV TME2 toxic membrane protein. De Beeck et al. teach TME2 transmembrane protein domain of HCV, which sequence is EYVVLLFLLLADARVCSCLWMMLLIAQAEA and differs from present SEQ ID NO: 2 at two amino acid residues MEYVVLLFLLLADARVCSCLWMMLLISQAEA (see Figure 1). It is noted that the claims read on a peptide of at least 2 amino acids within the SEQ ID NO: 2, as mentioned above.

Arechaga et al. teach expression of membrane proteins and their toxicity to E. coli (see the entire document). The reference by Ciccaglione et al. is cited to provide evidence that HCV E1 and E2 comprising transmembrane domains TME1 and TME2 were known to be toxic when expressed in the expression vector replicating in the E. coli cell (see the entire document).

It would have been obvious to the person of ordinary skill in the art to provide a bacterial expression system comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro and a nucleotide sequence encoding the HCV TME2 toxic membrane protein.

One would have been motivated to express De Beeck's toxic HCV TME2 membrane domain in Bolling's bacterial expression vector comprising in the 5' -3' direction a nucleotide sequence encoding the dipeptide Asp-Pro, because Bolling's has shown to successfully express toxic membrane protein gp41 in his expression system. Because the TME2 membrane protein was known to be toxic to E. coli cells, one would have been motivated to express the TME2 membrane protein in Bolling's expression system in which toxic membrane proteins such as gp41 have been successfully expressed.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolling et al. (US Patent 5,322,769) in view of De Beeck et al. (Journal of Biological Chemistry, 2000, Vol. 275, p. 31428-31437, in IDS of 6/23/2005) and Arechaga et al. (FEBS, 2000, Vol. 482, p. 215-219) as evidenced by Caccaglione et al. (Virus Genes, 2000, Vol. 21, p. 223-226, in IDS of 6/23/2005) as applied to claim 1 and further in view of Smith et al. (Gene, 1988, Vol. 67, p. 31-40) and Fiaschi et al. (FEBS, 1995, Vol. 367, p. 145-148).

Claims are drawn to an expression system encoding a soluble protein glutathione S-transferase and pGEXKT vector.

Bolling, De Beeck, Caccaglione and Arechaga teach the claim limitations as discussed above. The references do not teach soluble protein glutathione S-transferase or the pGEXKT vector.

Smith et al. teach that soluble protein glutathione S-transferase allows for purification of the fusion proteins expressed in E. coli from crude bacterial extracts (see the entire document). Fiaschi et al. teach the pGEXKT vector for expression of proteins in E. coli (see Materials and Methods).

It would have been obvious to express the soluble protein glutathione S-transferase (GST) upstream of the Asp-Pro sequence in order to allow the purification of the TME2 membrane protein from E. coli crude extract. It would have been obvious to express the TME2 membrane protein in the pGEXKT vector because the pGEXKT vector has been used in the art for expression of proteins of interest as evidenced by Fiaschi.

One would have been motivated to use Fiaschi's pGEXKT expression vector and express Smith's soluble protein GST upstream of Bolling's Asp-Pro sequence in order to allow the purification of De Beeck's TME2 membrane protein from E. coli crude extract.

One would have has a reasonable expectation of success to generate the pGEXKT bacterial expression vector comprising soluble protein GST upstream of the Asp-Pro sequence and to purify the expressed TME2 protein because the GST has been widely used in the art in the expression systems for fusion proteins as evidenced by Smith et al. Thus addition of the known

soluble protein GST upstream of the Asp-Pro sequence of the present construct would have yield predictable results.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AB

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 12-4-2007
Primary Examiner, TC1600